Remarks

Claims 1-29 are pending. New claim 30 has been added. The new claim finds support in the specification and claims as originally filed. No new matter is being added. Claims 1-24 and 29 are rejected and claims 25-28 are withdrawn from consideration. Each of the rejections is addressed below.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-24 and 29 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The rejected claims are directed to compositions comprising an enzyme and an immunogen for the treatment or prophylaxis of autoimmune conditions, such as rheumatoid arthritis, and kits comprising such compositions. For the reasons detailed below, Applicant respectfully disagrees with the enablement rejection and requests that it be withdrawn.

The standard set forth for enablement in 35 U.S.C. 112, first paragraph, requires that Applicant provide a description of the invention sufficient "to enable any person skilled in the art to which it pertains...to make and use" the invention. The examples provided in the specification clearly teach one of skill in the art how to make compositions containing an enzyme and an immunogen for the treatment of an autoimmune disorder. Specifically, Applicant describes a composition comprising the enzyme, β-glucuronidase, and the immunogen, type II collagen (page 9, 4th paragraph). Compositions containing the enzyme and the immunogen were injected into a widely accepted mouse model of rheumatoid arthritis, where the onset (e.g., at low dose) was delayed and the severity (e.g., at high dose) of arthritis was reduced based on results in a blinded study.

Specifically, Applicant states, "Animals were scored for clinical arthritis from day 17 to day 52 twice weekly by observation of joint redness and swelling. The study centre was blinded (page 9, 4th paragraph)." The features scored in the blinded study included joint swelling, redness, inflammation, and bone remodeling (page 11, 4th paragraph). In the low dose treatment group, a statistically significant difference in onset and arthritis severity was observed at day 29 (Figures 2 and 3, and page 12, second paragraph). Applicant discovered that the claimed composition "altered the course of arthritis in the experiment" by delaying arthritis progression (page 13, 1st paragraph). Significantly, this alteration in the progression of the disease occurred

after a single treatment. Based on these results, it is likely that increased protection would be observed if further doses were given (page 13, 1st paragraph).

The severity of arthritis observed in mice that received a higher dose of the claimed composition was also significantly lessened. Applicant found that disease in the group that received the higher dose was much lower than expected, and was statistically significant (page 12, 4th paragraph). Regarding these results, Applicant states, "The alteration to the course of disease observed following high dose treatment is suggestive of a **potent anti-arthritic effect** (page 13, 4th paragraph; emphasis added)." In fact, following treatment with the claimed compositions, Applicant found that levels of disease reduction were comparable to those observed when established anti-arthritic drugs were given (page 13, 4th paragraph).

In view of this disclosure, the specification clearly contains a description of "how to make" the invention (e.g., page 3, line 9 - page 5, line 28 of the originally filed specification) and "how to use" the invention (e.g., page 2, line 31 – page 3, line 8; and page 5, line 29 – page 6, line 18 of the originally filed specification). Thus, the disclosures of the specification support the standard of enablement set forth in the first paragraph of 35 U.S.C. 112.

In support of the enablement rejection, the Examiner states that "The data regarding groups B and C is not clear cut." Applicant respectfully disagrees. Applicant has presented a statistical analysis of the data at day 52 post induction in Figure 5, which indicates that group C and group B differ significantly. The likelihood that the two groups would differ in this way by random sorting is low, as shown in the calculated p value ($p<0.003$) (Figure 5). These results clearly indicate that group C, which received 50 ng/ml collagen and glucuronidase, showed a reduction in the severity of arthritis compared to group B, which received buffer control, and this effect can be statistically relied upon. Furthermore, Applicants respectfully disagree with the Examiner that "There is no substantial difference between the control group and those mice receiving the lower does [sic] (group A) (Office action mailed October 15, 2007, page 4, 2nd paragraph)."

Contrary to the Examiner's assertion, Figure 2 shows a clear delay in onset of disease. Arthritis onset was delayed by about 7 days in group A mice, which received 50 fg/ml collagen and glucuronidase, compared to group B control mice (Figure 2). Additionally, in Figure 3, a

marked reduction in disease severity was observed in mice treated with 50 fg/ml collagen and glucuronidase relative to control mice (page 10, fourth paragraph). A statistical comparison between groups A and B provided a calculated p value of <0.033 (Figure 3). This result indicates that the likelihood is low that the observed effect is due to random sampling or is merely coincidental. It should be borne in mind that rheumatoid arthritis is a disease with a very slow and progressive onset and as such any delay in onset is a useful treatment of the disease. Based on these results, a person of skill in the art would reasonably conclude that the invention would be useful in treating or preventing autoimmune diseases.

In support of the enablement rejection, the Examiner has cited two articles by Terr ("Unproven and Controversial Forms of Immunotherapy." Clinical Allergy and Immunology (2004) 18: 703-710 (hereinafter "Terr"), and "Unproven and Controversial Forms of Immunotherapy." Clinical Allergy and Immunology (1999) 12:479-488). Each of these articles provides a review of therapies that Terr considers unconventional or controversial. Neither of these articles refutes the probative evidence provided by Applicant's disclosure.

With respect to the use of the enzyme, β-glucuronidase, in combination with an immunogen, Terr states that "To date, there have been no published research findings in patients treated by this method to substantiate this theory." Terr further states that "the presumed pharmacological property of β-glucuronidase on the immune system are based on anecdotal evidence only." Terr's criticism that the therapy is unsupported by scientific evidence is overcome by the probative data disclosed in the specification, which would lead one of skill in the art to conclude that the claimed compositions are useful in treating or preventing autoimmune diseases, such as rheumatoid arthritis.

The claimed compositions are enabled by the examples present in the specification, which describe how to make and use a composition comprising an enzyme and an immunogen in *in vivo* experiments in an animal model of an autoimmune disease (pages 8-13). The Examiner questions the reliability of Applicant's data, stating that "the data presented by the specification does not appear to be a reliable indicator that the skilled artisan could use to a predict successful therapeutic outcome for a patient group that is known to be extremely difficult to treat (Office action mailed October 15, 2007, page 5, 1st paragraph)." Applicant invites the Examiner's

attention to *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971), where the court states:

> [I]t is incumbent upon the Patent Office . . . to explain ***why*** it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is **inconsistent with the contested statement**. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure. 439 F.2d at 224, 169 USPQ at 370 (Emphasis added).

In the present case, the Examiner apparently relies on Terr to provide the requisite evidence or reasoning to show that Applicant's invention lacks enablement; however, this reliance is misplaced. Terr provides no evidence or reasoning that is inconsistent with Applicant's disclosure. Terr stands for the principle that therapeutic methods must be based on objective scientific data. Applicant's disclosure of a blinded study showing treatment of an autoimmune disease with the claimed composition provides just such objective scientific data. Thus, Terr fails to support the lack of enablement rejection.

The Examiner appears to question whether Applicant's results in an animal model of autoimmune disease would be predictive of results in human therapy. Where Applicants disclose a working example, this fact weighs heavily in favor of enablement. M.P.E.P. §2164.02 states:

> An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention . . . the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).

The Examiner has failed to show why Applicant's disclosed results in an animal model would fail to correlate with autoimmune disease.

M.P.E.P. §2164.02 is clear that "Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example." The Examiner has not provided any reason to doubt the mouse model of rheumatoid arthritis described by Applicant. Furthermore, M.P.E.P. §2164.02 elaborates that "a rigorous or an invariable exact correlation is not required," citing *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):

> [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and **therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence.** (Citations omitted.) [Emphasis added]

The Examiner has not provided a reason to doubt the mouse model of autoimmune disease used to obtain the *in vivo* data disclosed in Applicant's specification. For the reasons detailed above, there is no reason why the compositions and methods being claimed would not be expected to work as described. Applicants have clearly satisfied the enablement requirement. In view of the above evidence and arguments, Applicants request that the enablement rejection be withdrawn.

CONCLUSION

In view of the above amendment and response, Applicants believe the pending application is in condition for allowance.

Applicants believe that no additional fee is due to consider the present amendment. Nevertheless, the Director is hereby authorized to charge or credit any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105.

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Respectfully submitted,

By _____

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